UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

March 6, 2002

MEMORANDUM:

SUBJECT: **Propiconazole** (122101): Reassessment of poultry and egg tolerances.
DP Barcode: D281520
Reregistration Case: 3125

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TO: Eric Olson, CRM
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Special Review and Reregistration (7508C)

In preparation for the Residue Chemistry Chapter for the Propiconazole Reregistration Eligibility Decision (RED), HED is conducting a reassessment of currently established tolerances for the combined residues of propiconazole and its metabolites determined as 2,4-dichlorobenzoic acid in poultry commodities and egg.

EXECUTIVE SUMMARY:

Permanent tolerances are established for the combined residues of propiconazole and its metabolites determined as 2,4-dichlorobenzoic acid and expressed as parent compound in poultry fat (0.1 ppm), poultry kidney (0.2 ppm), poultry liver (0.2 ppm), poultry mbyp except kidney and liver (0.1 ppm), poultry meat (0.1 ppm), and eggs (0.1 ppm) [40 CFR §180.434]. Based on the available residue chemistry data (poultry metabolism and feeding studies), there is no reasonable expectation of finite propiconazole residues of concern in poultry commodities and eggs resulting from the registered uses of propiconazole. Currently established poultry and egg tolerances (as indicated above) should be revoked.

BACKGROUND

Propiconazole [1-[[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl]-1H-1,2,4-triazole] is one of the systemic broad-spectrum fungicides from the triazole class known to have both protective and curative properties effective against mildews and rusts in vegetables, cereals, deciduous fruit, grapes and ornamentals. Currently registered food/feed uses of propiconazole subject to reregistration are for treatment of fungal disease in bananas and plantains, barley, celery, corn (field, pop and sweet), grasses grown for seed, mint, mushrooms (as a wood treatment), oats, peanuts, pecans, pineapple (as a seed piece treatment), rice, rye, stone fruits, sugarcane (as a seed piece treatment), wheat, and wild rice.

Section 18 Exemptions with associated tolerances have been issued for food/feed uses of propiconazole on almonds, blueberries, cranberries, dry beans, raspberries and sorghum. There are also a number of pending uses of propiconazole under review in the Agency.

Permanent tolerances are established for the combined residues of propiconazole and its metabolites determined as 2,4-dichlorobenzoic acid and expressed as parent compound in/on various plant and animal commodities [40 CFR §180.434]. In addition, time-limited Section 18 tolerances, due to expire between 7/31/00 and 03/30/04, are currently established for almond hulls (2.5 ppm), almond nutmeats (0.1 ppm), blueberries (1.0 ppm), cranberries (1.0 ppm), dry bean forage (8.0 ppm), dry bean hay (8.0 ppm), dry beans (0.5 ppm), raspberries (1.0 ppm), aspirated grain fractions derived from sorghum (20 ppm), sorghum grain (0.2 ppm), and sorghum stover (1.5 ppm) [40 CFR §180.434(b)].

Adequate GC/ECD methods are available for enforcement and data collection purposes in plant and animal commodities. The enforcement methods have been successfully validated by EPA and have been submitted to FDA for publication in the Pesticide Analytical Manual (PAM), Vol. II for enforcement of propiconazole tolerances, as currently expressed. The methods use a single moiety detection in which residues of propiconazole and its metabolites containing the 2,4-dichlorophenyl moiety are converted to 2,4-dichlorobenzoic acid (2,4-DCBA) methyl ester and are reported as propiconazole equivalents.

DETAILED CONSIDERATIONS

A. Maximum Theoretical Dietary Burden Calculation for Poultry

The reviewer has determined that the combined residues of propiconazole and its metabolites determined as 2,4-dichlorobenzoic acid and expressed as parent compound (hereafter referred to as "total" propiconazole) resulting in/on wheat grain and peanut meal from use of propiconazole to wheat and peanuts are likely to be the greatest contributors to the maximum theoretical dietary burden for poultry and has estimated the maximum residue levels in/on these feed items based on the best available information. The reviewer estimates the maximum residue levels of "total" propiconazole in/on wheat grain and peanut meal at 0.3 ppm and 0.5 ppm, respectively. [Note:

These estimates are higher than the currently established tolerance levels in/on wheat grain (0.1 ppm) and peanuts (0.2 ppm).]

For wheat grain, the estimated maximum "total" propiconazole residue level is based on a proposed maximum use rate of propiconazole to wheat for the harvest of grain and straw (2 applications at 0.11 lb ai/A/application with the last application at Feekes Growth Stage 10.5) and available wheat field trial data (MRID 44757208) which are currently under review.

For peanut meal, the estimated maximum "total" propiconazole residue level is based on the currently established tolerance for peanuts (0.2 ppm) and the maximum theoretical concentration factor for peanut meal (2.2x). Peanut meal processing data are not available and although available peanut processing data, taken as a whole, do not suggest the potential for significant concentration of "total" propiconazole residues in peanut meal, the maximum theoretical concentration factor for peanut meal has been used here as a conservative measure.

The maximum theoretical dietary burden for poultry is estimated at 0.4 ppm. See Table 1 below for details.

Table 1. Calculation of maximum theoretical dietary burden for poultry.

Feed Commodity	Estimated Maximum "Total" Propiconazole Residue Level (ppm)	% Dry Matter	% of Diet	Burden (ppm)
Wheat, grain	0.3	89	80	0.3
Peanut, meal	0.5	86	20	0.1
		TOTAL	100	**0.4**

B. Poultry Residue Chemistry Data

1. Phenyl-labeled Metabolism Study

Study Citation: **41823302** Doweyko, A. (1990) Metabolism of Phenyl [carbon 14]Propiconazole in Chickens: Lab Project Number: F-00051. Unpublished study prepared by Ciba-Geigy Corp. 71 p.

Agency Review of Study: PP#1F3974 by S. Willett (6/11/91).

Study Summary: Four laying hens were fed [^{14}C]phenyl-labeled propiconazole for 8 consecutive days at a rate estimated at 67 ppm in feed. This dose level represents 168x the maximum theoretical dietary burden for poultry. Residues in eggs plateaued by Day 7. Total radioactive residue (TRR) levels found in tissue and egg samples are provided in Table 2 below.

Table 2: Summary of TRR levels found in poultry tissue and egg samples from the poultry metabolism study.

Commodity	TRR Range (ppm)	Average TRR (ppm)
Kidney	3.33 - 5.27	4.19
Liver	3.24 - 4.98	3.94
Gizzard	1.20 - 3.75	2.38
Crop	0.92 - 4.51	2.28
Peritoneal Fat	0.72 - 1.11	0.98
Heart	0.52 - 0.92	0.71
Blood	0.47 - 0.96	0.69
Skin/Fat	0.47 - 0.68	0.59
Thigh Muscle	0.26 - 0.59	0.40
Breast Muscle	0.23 - 0.46	0.33
Egg Whites	nd - 1.50	0.70 (highest daily average)
Egg Yolks	nd - 2.08	1.67 (highest daily average)

2. Feeding Study

Study Citation: **00137861** Ciba-Geigy Corp. (1984) [Residue: CGA-64250–Rice]. Compilation; unpublished study received Apr 6, 1984 under 4F3074; CDL: 072556-A; 072557).

Agency Review of Study: PP#4F3074 by A. Smith (7/12/84).

Study Summary: Laying hens were fed propiconazole daily at dose levels of 7.5, 37.5, and 75 ppm for periods of 14, 21, or 28 days. These dose levels represent 18x, 93x, and 187x the maximum theoretical dietary burden for poultry. Egg samples were collected daily. Hens were sacrificed at weekly intervals and breast plus thigh, liver, fat, and skin samples were taken for analysis. All tissue and egg samples were analyzed for the combined residues of propiconazole and its metabolites determined as 2,4-dichlorobenzoic acid and expressed as parent compound (hereafter referred to as "total" propiconazole). Some samples were analyzed for residues of propiconazole *per se*.

Analytical Method No. AG-354 (GC/FID) was used to determine residues of propiconazole *per se* in some tissue and egg samples. These results will not be discussed further.

Analytical Method No. AG-359 (GC/ECD) was used to determine residues of "total" propiconazole in all tissue and egg samples. In brief, samples were extracted with acetonitrile (egg samples) or acetonitrile/water solution (tissue samples) and filtered. An aliquot of the filtrate was washed with hexane and residues were partitioned into acetonitrile and the acetonitrile phase was evaporate. The resulting aqueous solution was treated with concentrated nitric acid and partitioned with a hexane/ethyl ether mixture which was evaporated to dryness. The residue was treated with diazomethane solution forming the methyl derivative of dichlorobenzoic acid. The solvent was evaporated and the residue was cleaned up on a silica gel column and eluted with an ethyl ether/hexane solvent mixture. (For liver samples an additional cleanup with aluminum oxide column was required.) The eluate was concentrated, and the residue was determined by gas chromatography using an electron capture detector. Residues were expressed as the parent compound. The limit of determination was reported as 0.10 ppm for liver and 0.05 ppm for eggs and other tissues.

Control poultry tissue and egg samples were fortified with propiconazole *per se* at levels of 0.05-1.0 ppm. Overall recoveries were 51-91%.

No "total" propiconazole residues (<0.05 ppm) were found in egg samples from the 7.5 ppm feeding level. The highest "total" propiconazole residue levels found in egg samples from the 37.5 ppm and 75 ppm feeding levels were 0.18 ppm and 0.37 ppm, respectively. A summary of the highest "total" propiconazole residue levels found in poultry tissue samples is provided in Table 3 below.

Table 3. Residues of "total" propiconazole in tissues of laying hens fed propiconazole at dose levels of 7.5, 37.5, and 75 ppm generated with Method AG-359.

	Feeding level (ppm)								
	14 days			21 days			28 days		
Matrix	7.5	37.5	75	7.5	37.5	75	7.5	37.5	75
Muscle	<0.05	<0.05	<0.05	<0.05	<0.05	0.07	<0.05	<0.05	0.06
Liver	<0.10	0.10	0.47	<0.10	<0.10	0.39	<0.10	0.16	0.30
Fat	<0.05	<0.05	0.11	<0.05	<0.05	0.06	<0.05	<0.05	0.05
Skin	<0.05	<0.05	0.05	<0.05	<0.05	0.07	<0.05	0.05	0.06

3. Data Collection Method AG-359

Study Citation: **40150701** Cheung, M. (1987) Response to EPA's Concern Regarding the Validity of Analytical Method AG-359 to Determine Propiconazole Residues in Animal Commodities: 2,4-Dichlorobenzoic Acid by Capillary Gas in Animal Commodities: (Magnitude of Residues): Lab Study No.: ABR-87039. Unpublished study prepared by Ciba-Geigy Corp. 624 p.

Agency Review of Study: CB No. 2172 by S. Malak (5/14/87).

Agency Issues/Conclusions: Subsequent to the Agency's review of the poultry feeding study generated with method AG-359 (memo by A. Smith dated 07/12/84) which was summarized above, the Agency re-evaluated the poultry feeding study data results (memo by S. Malak and W. Chin dated 03/20/87) along with available ruminant feeding study data in light of concerns raised when method AG-359 failed the method validation trial for enforcement purposes and determined that "because of the poor resolution of method No. AG-359 used to determine propiconazole residues in animal commodities, all the residue data of animal commodities generated from this method are considered invalid". Later the registrant submitted analytical method trial data (MRID 40150701) in which some of the test samples collected in the livestock feeding studies (some ruminant tissue and egg samples) were re-analyzed using an improved version of method AG-359, method AG-517 which has been deemed adequate for animal tolerance enforcement purposes (see discussion under Section D below). The Agency reviewed these method trial data (memo by S. Malak dated 05/14/87) and found that despite the prolonged period of frozen storage, "total" propiconazole residue levels in test samples determined with enforcement method AG-517 were generally higher than the residue levels determined 6 years prior in the same test samples with method AG-359. However, after further re-evaluation (memo by S. Malak dated 05/14/87) of the residue data generated using method AG-359 (raw data and sample chromatograms of control, fortified, and treated samples) the Agency finally concluded that method AG-359 "may be used to collect residue data by experienced personnel familiar with the technique" and that the available livestock residue data generated using method AG-359 are valid.

C. Estimated Maximum Residue Levels in Poultry Tissues and Eggs

No combined residues of propiconazole and its metabolites determined as 2,4-dichlorobenzoic acid (hereafter referred to as "total" propiconazole) were found at levels above the LOQ of the analytical method in poultry muscle, liver, fat and egg samples collected from hens feed propiconazole at rates >10x the maximum theoretical dietary burden for poultry. Based on the available residue chemistry data (poultry metabolism and feeding studies), there is no reasonable expectation of finite residues of "total" propiconazole in poultry commodities and eggs resulting from the currently registered uses of propiconazole.

Table 4. Estimated Maximum "Total" Propiconazole Residue Levels in Poultry Tissues and Egg Resulting from the Maximum Theoretical Dietary Burden for Poultry.

Matrix	Poultry Metabolism Study (ppm)		Poultry Feeding Study (ppm)			
	Average TRR Found at 67 ppm (168x) Feeding Rate	Estimated Maximum Residue at 1x Feeding Rate	Highest Residue Found at 7.5 ppm (18x) Feeding Rate	Highest Residue Found at 37.5 ppm (93x) Feeding Rate	Highest Residue Found at 75 ppm (187x) Feeding Rate	**Estimated Maximum Residue at 1x Feeding Rate**
Muscle	0.40	<0.01	<0.05	<0.05	0.07	**<0.01**
Liver	3.94	<0.03	<0.10	0.16	0.47	**<0.01**
Fat	0.98	<0.01	<0.05	<0.05	0.11	**<0.01**
Egg	1.67 [1]	<0.01	<0.05	0.18	0.37	**<0.01**
Kidney	4.19	<0.03	Not Analyzed			

1 Highest average daily TRR in egg yolk.
Note: The LOQ of the enforcement method is 0.05 ppm for poultry tissues and egg.

D. Residue Analytical Enforcement Methods - Animal Commodities

Residue methods AG-517 and AG-629 (a modification of method AG-517) are available for determination of propiconazole and its metabolites containing the 2,4-dichlorophenyl moiety in animal commodities using gas chromatography and electron capture detection. The methods use a single moiety detection in which residues are converted to 2,4-dichlorobenzoic acid (DCBA), determined as the 2,4-DCBA methyl ester, and reported as propiconazole equivalents using a conversion factor of 1.79. The method LOQ is 0.05 ppm for residues in meat, poultry, and eggs and 0.02 ppm for residues in milk. Method AG-517 has undergone radiovalidation and was successfully validated by the Agency. Because method AG-629 differs only in the use of methyl iodide instead of diazomethane as the methylating agent, no independent or Agency laboratory validations are required. These methods have been forwarded to FDA for publication in PAM Vol. II for enforcement purposes.

NOTE: Samples from the poultry feeding study were analyzed using method AG-359 (an early

version of method AG-517) and later with method AG-517.

E. International Considerations

The Codex Alimentarius Commission has established several maximum residue limits (MRLs) for propiconazole in/on various raw agricultural commodities. The Codex MRLs are expressed in terms of propiconazole *per se*. The Codex MRLs and the current U.S. tolerances are incompatible with respect to tolerance expression; the current U.S. tolerances for plant and animal commodities are expressed in terms of the combined residues of propiconazole and its metabolites determined as 2,4-dichlorobenzoic acid and expressed as parent compound. A numerical comparison of the Codex MRLs and the corresponding current U.S. tolerances in livestock commodities **only** is presented in the table below.

Table 5: Codex MRLs for Propiconazole in livestock commodities **only** and applicable current U.S. tolerances.

Codex			Current U.S. Tolerance (ppm)
Commodity (As Defined)	MRL (mg/kg)	Step	
Edible offal (mammalian)	0.05	CXL	0.1
Eggs	0.05 (*)	CXL	0.1
Meat (from mammals other than marine)	0.05 (*)	CXL	0.1
Milks	0.01 (*)	CXL	0.05
Poultry meat	0.05 (*)	CXL	0.1

Note: Asterisk designates that the MRL is set at the limit of quantitation.

cc: BLCKohlligian (RRB4), Propiconazole Phase 4 File, RF.
RD/I: RRB4 ResChem Team (03/13/02) SHummel (03/13/02) ChemSAC (03/27/02)
7509C:RRB4:BLCKohlligian:CM#2:Rm 712N:703-305-7462:03/06/02.